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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,409	11/07/2005	Markku Sakari Kulomaa	3502-1073	7497

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EXAMINER	
LEE, JAE W	
ART UNIT	**PAPER NUMBER**
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,409	KULOMAA ET AL.	
	Examiner	Art Unit	
	Jae W. Lee	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-20 and 22-27* is/are pending in the application.

4a) Of the above claim(s) *11, 13, 17, 18, 20, 23 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6-10, 12, 14-16, 19, 22, 24, 25 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/27/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application status

Preliminary amendments for claims 1, 6-8, 13-16 and addition of new claims 22-27, filed on 12/15/2006, are acknowledged. Applicants have cancelled Claims 2-5 and 21, amended Claims 1, 6-8, 13-16, and added new Claims 22-27.

Claims 1, 6-20 and 22-27 are pending in this application.

Priority

A claim of priority to the PCT/FI03/00619, filed on 08/22/2003, and Foreign application FINLAND 20021518, filed on 08/22/2003, is acknowledged.

Election

Applicant's election without traverse of Group I, Claims 1-20, is acknowledged. Applicants however traversed species election of amino acid mutation positions 86, 106 and 117. The traversal is on the ground(s) that claims share the same technical feature because "common inventive concept is considered to be improved properties via the enhanced covalent binding of the four molecules of the biotin binding tetramer."

In response to Applicant's traversal, the Examiner finds Applicant's argument not persuasive because Applicants do not address the traversal with respect to the previous Office Action which addressed why they do not share the common inventive concept in view of Laitinen et al. which teach a mutant of biotin binding protein from avidin-related

genes in Chicken. Furthermore, they do not share the "special technical feature" because, for instance, the invention of Claim 8 has mutations at positions 86 and 106, and Claim 19 has a single mutation at position 124. Therefore, Claims 8 and 19 do not share the same "special technical feature," i.e., specific mutation, and they are mutually exclusive, in addition to being non-obvious variants.

It is noted by the Examiner that Claims 1, 6-20 and 22-27 are subjected to further restriction requirement under 35 U.S.C. 121.

Therefore, election is required of one of inventions (A)-(E) if applicant decides to elect any one of inventions I-II from the previous restriction mailed on 11/15/2006.

(A) AVR 1 corresponding to SEQ ID NO: 3

(B) AVR 2 corresponding to SEQ ID NO: 4

(C) AVR 3 corresponding to SEQ ID NO: 5

(D) AVR 4 corresponding to SEQ ID NO: 6

(E) AVR 5 corresponding to SEQ ID NO: 7

Each AVR proteins are related but patentably distinct products because AVR proteins are structurally different having different amino acid sequences as they are represented by different SEQ ID NOs. Therefore, where structural identity is required, such as for hybridization or expression, the different sequences of different proteins have different effects. Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions require a different of search for each AVR protein

and its corresponding sequence (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

Applicant's attorney, Bob Madsen, has also agreed to a telephonic election of AVR 4 and 5 corresponding to SEQ ID NO: 6 and 7, respectively, with traverse on 3/2/2007. Although Applicants did not elect a single AVR with a corresponding SEQ ID NO, Applicants allege that SEQ ID NO: 6 and 7, therefore AVR 4 and 5, are closely related with 99% sequence identity. As such, the Examiner accepted the Applicant's election of AVR 4 and 5 corresponding to SEQ ID NO: 6 and 7.

Claims 11, 13, 17, 18, 20, 23 and 26, AVR 1, 2, 3, 6 and 7, and mutation positions 43 and 124 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claims 1, 6-10, 12, 14-16, 19, 22, 24, 25 and 27, and AVR 4 and 5 with mutations at positions 86, 106 and 117 will be examined on the merits.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Objections to the Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, Applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See particularly Figures 4 and 9 of the specification containing amino acid sequences, and therefore those Figures should have proper sequence identifiers for the amino acid sequences in either those Figures or in the brief description of the drawings.

Appropriate correction for each error is required.

Claim Objections

Claims 12, 19, 24 and 27 are objected to because of the following informalities:

Claims 12, 19, 24 and 27 contain non-elected inventions, i.e., AVR 3 and 6, 7, and mutation position 124.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6-10, 12, 14-16, 19, 22, 24, 25 and 27 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 6-10, 12, 14-16, 19, 22, 24, 25 and 27 are drawn to a genus of any mutant of biotin binding proteins having any improved properties compared to the wild type protein, wherein the mutant has six intermonomeric disulphide bridges anywhere in the tetramer, and the protein is selected from the group comprising chicken avidin,

bacterial streptavidin, other poultry avidin, such as avidin protein from duck, goose, ostrich or turkey, and chicken avidin-related proteins (AVRs).

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of [compositions or methods], it must be clear that: (1) the identifying characteristics of the claimed [compositions or methods] have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed.

The specification discloses examples of chicken AVR mutants comprising SEQ ID NO: 6 or 7 having 1) a single mutation at amino acid position 117 to cysteine, 2) double mutation at amino acid positions 86 and 106 to cysteine, and 3) triple mutation at amino acid positions 86, 106 and 117. However, this is an inadequate written description for a genus of biotin binding mutant proteins, wherein the mutant has six intermonomeric disulphide bridges at any location bridging any one monomer with another, wherein the protein is from bacterial streptavidin, other poultry avidin such as avidin protein from duck, goose, ostrich or turkey.

Claim 1 is drawn to a genus of any mutant of biotin binding proteins having any improved properties compared to the wild type protein, wherein the mutant has six intermonomeric disulphide bridges anywhere in the tetramer, and the protein is selected from the group comprising chicken avidin, bacterial streptavidin, other poultry avidin,

such as avidin protein from duck, goose, ostrich or turkey, and chicken avidin-related proteins (AVRs).

The specification, however, does not provide a disclosure of any particular structure to function/activity relationship between any mutant of biotin binding proteins. The specification also lacks description with respect to what function, if any, is required for any mutant of biotin binding proteins, in addition to what those "improved properties" are, for a genus of such mutants.

The specification provides examples of a method, comprising the use of chicken avidin-related proteins (AVR 4 and 5). However, this is inadequate written description for a genus of mutants of biotin binding proteins from bacterial streptavidin, other poultry avidin, such as avidin protein from duck, goose, ostrich or turkey.

Further, the specification does not adequately describe a genus of biotin binding proteins having six intermonomeric disulphide bridges at any location bridging any one monomer with another.

Given the lack of additional representatives of a genus of any mutant of biotin binding proteins having any improved properties compared to the wild type protein, wherein the mutant has six intermonomeric disulphide bridges anywhere in the tetramer, and the protein is selected from the group comprising chicken avidin, bacterial streptavidin, other poultry avidin, such as avidin protein from duck, goose, ostrich or turkey, and chicken avidin-related proteins (AVRs) as encompassed by the claim, Applicants have failed to sufficiently describe the claimed invention, in such full, clear,

concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1, 6-10, 12, 14-16, 19, 22, 24, 25 and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, because the specification, while being enabling for chicken AVR mutants comprising SEQ ID NO: 6 or 7 having 1) a single mutation at amino acid position 117 to cysteine, 2) double mutation at amino acid positions 86 and 106 to cysteine, or 3) triple mutation at amino acid positions 86, 106 and 117, does not reasonably provide enablement for any mutant of biotin binding protein having any improved properties compared to the wild type protein, wherein the mutant has six intermonomeric disulphide bridges anywhere in the tetramer, and the protein is selected from the group comprising chicken avidin, bacterial streptavidin, other poultry avidin, such as avidin protein from duck, goose, ostrich or turkey, and chicken avidin-related proteins (AVRs). Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Claims 1, 6-10, 12, 14-16, 19, 22, 24, 25 and 27 are so broad as to encompass any mutant of biotin binding protein having any improved properties compared to the wild type protein, wherein the mutant has six intermonomeric disulphide bridges anywhere in the tetramer, and the protein is selected from the group comprising chicken avidin, bacterial streptavidin, other poultry avidin, such as avidin protein from duck, goose, ostrich or turkey, and chicken avidin-related proteins (AVRs).

The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the "mutant of a biotin binding protein". Since the amino

acid sequence of a peptide determines its structural and functional properties, predictability of which peptides can be used while obtaining the desired function requires a knowledge of and guidance with regard to which amino acids in the peptide's sequence, if any, are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the peptide's structure relates to its desired function. In addition, the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of different peptides/proteins. The specification, however, only discloses amino acid sequence of SEQ ID NO: 6 or 7.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any mutant of biotin binding protein, wherein the protein is selected from the group comprising chicken avidin, bacterial streptavidin, other poultry avidin, such as avidin protein from duck, goose, ostrich or turkey, and chicken avidin-related proteins (AVRs) because the specification does not establish: (A) regions of the protein structure which may be modified without affecting

the desired activity of the mutant protein; (B) regions of the protein structure which may be modified without affecting the improved properties of the mutant protein (see 112 2nd paragraph rejection); (C) specific locations of cysteine residues that must be mutated, which are required for six intermonomeric disulphide bridges; (D) the general tolerance of the mutant protein to modification and extent of such tolerance; (E) a rational and predictable scheme for modifying any amino acid residue of the mutant protein with an expectation of obtaining the desired biological function; and (F) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Because of this lack of guidance, and the fact that the relationship between the polypeptide sequence of a protein and its activity/function is not well understood and unpredictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), it would require undue experimentation for one skilled in the art to make and use any mutant of biotin binding protein having any improved properties compared to the wild type protein, wherein the mutant has six intermonomeric disulphide bridges anywhere in the tetramer, and the protein is selected from the group comprising chicken avidin, bacterial streptavidin, other poultry avidin, such as avidin protein from duck, goose, ostrich or turkey, and chicken avidin-related proteins (AVRs).

Notes on references related to prior art of the invention:

1. Chilkoti et al., Engineered Chimeric Streptavidin Tetramers as Novel Tools for Bioseparations and Drug Delivery, Biotechnology 13, 1198 - 1204 (1995).

2. Laitinen et al., Chicken avidin-related proteins show altered biotin-binding and physico-chemical properties as compared with avidin, Biochem. J. (2002) 363, 609-617.

Conclusion

Claims 1, 6-10, 12, 14-16, 19, 22, 24, 25 and 27 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

The instant Office action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen K. Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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PRIMARY EXAMINER